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The Case for Thoughtful Prescribing of Proton Pump Inhibitors in Infants.

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Authors

Rosen, Rachel L
Krishnan, Usha
Mousa, Hayat
et al.

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Proton Pump Inhibitors May Not Be the First Line of Treatment for GERD in Infants

Thirumazhisai S. Gunasekaran, Samir Kakodkar, and James H. Berman
Advocate Children's Hospital, Loyola Medical Cneter, University of Illinois, Chicago, IL

To the Editor: We applaud Krishnan et al (1) for the ESPGHAN-NASPGHAN guidelines on ''The evaluation and treatment of gastrointestinal and nutritional complications in children with Esophageal atresia /Tracheoesophageal fistula.''

We agree on the recommendation of gastroesophageal reflux being treated with acid suppressants from the neonatal age, though the evidence is not strong. We wish to bring to attention some special considerations when prescribing proton pump inhibitor (PPI) in the first 12 months of age and more so for the first 6 months.

A strong case exists for the cautious use of PPIs in infants, more so in infants less than 6 months of age. The pharmacokinetics (pK) of PPIs in infants differs compared with older children and adults. Springer et al (2) showed that for the same dose of lansoprazole, infants less than 10 weeks of age had 5 times higher plasma total exposure and area under the curve (AUC) of lansoprazole compared with infants older than 10 weeks. This extreme variable plasma level of lansoprazole was also supported by Tran et al's (3) study; 2 infants, 18 days and 3.2 months old on lansoprazole 17 mg/m^2 per day, had the longest half-life ($t_{1/2}$) and the highest AUC values and the lowest plasma clearance (CL/F) values. Another study by Anderson et al (4) reported the pK of omeprazole in 0 to 24-month-old children given a single dose of omeprazole 1 or 1.5 mg/kg showed increased exposure of omeprazole for infants less than 5 months, compared with children 5 to 24 months who had consistent levels. Omari et al (5) showed that in children 1 to 24 months given esomeprazole (0.25 and 1 mg/kg), children under 12 months had higher AUC and maximum plasma concentration at steady state (C_{SSmax}) compared with children older than 12 months. The authors commented that the maturation of the enzymes required for metabolism of PPIs (CYP2C19 and CYP3A4) is variable and the metabolism of esomeprazole may differ early versus late infancy. Pharmacokinetics also suggested that immaturity of renal clearance in early infancy may prolong the $t_{1/2}$ of drugs leading to higher PPI blood levels (4,5). Clearance of pantoprazole with increasing age, from 1 month through 6 years, was observed and there were no slow metabolizers within the infants in this group (6). These studies clearly demonstrate that infancy is a critical age and PPIs should be used with caution especially during the first 6 months of age. Additionally, no pre-made liquid preparation is available for many PPIs that can be easily administered, a risk for accurate dosing.

Further Krishnan et al (1) warn about the long-term adverse effects on the use of PPIs including change in microbiota, *C. difficile* colitis, acute gastroenteritis, community-acquired pneumonia, bone fractures, dementia, hypomagnesemia, and B12 deficiency. Importantly, infants less than 3 months of age are at increased risk for sequelae from infection with an immature immune system (7).

Because PPIs are effective treatment for severe GERD in children (8), PPIs are the drug of choice for GERD in EA-TEF children. In infants less than 12 months of age, particularly in the first 6 months, the practitioner should have a clear indication to use PPI and be cautious when prescribing PPI.

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The Case for Thoughtful Prescribing of Proton Pump Inhibitors in Infants

Reply: We appreciate the comments discussed in the letter by Drs Gunasekaran, Kakodkar, and Berman. Although the authors lay out the case for the differential pharmacokinetics of proton pump inhibitors in infants as a reason for cautious prescribing, we wanted to highlight that the main reason not to prescribe these medications in infants is because they are not efficacious in treating symptoms in otherwise healthy infants. Despite the fact that between 23% and 71% of infants are prescribed either an H2 antagonist or a proton pump inhibitor worldwide, there are multiple studies including placebo-controlled trials showing a lack of benefit of acid suppression in improving symptoms of fussing, crying, arching, apnea, cough, hoarseness, wheezing, or feeding intolerance (1–4). The lack of efficacy may be multifactorial; symptoms may not be reflux related or the reflux is a result of nonacidic gastric contents getting refluxed (ie, formula or breast milk) upon which acid suppression has no effect. So, although consideration of pharmacokinetics and side effects are important when prescribing, the biggest deterrent should be that these medications have consistently been shown not to improve symptoms.

There are 2 notable populations in whom acid suppression is warranted, those patients at high risk for esophagitis and those with confirmed histologic esophagitis with eosinophilic infiltrates. Children with esophageal motility disorders such as treated achalasia

or esophageal atresia fall into this first category; any reflux that enters the esophagus is poorly cleared because of profound disturbances of peristalsis. Recognizing the impact of dysmotility on poor reflux clearance is critical and, this population, we feel, merits aggressive acid suppression therapy with proton pump inhibitors to prevent long-term reflux complications including erosive esophagitis, metaplasia of esophageal epithelium, and stricturing (5). Apart from patients with dysmotility, a second population meriting therapy includes symptomatic infants with eosinophilic infiltration of the esophagus in whom proton pump inhibitor (PPI) therapy may help to narrow the differential diagnosis including eosinophilic esophagitis, proton pump inhibitor responsive eosinophilic esophagitis, and reflux esophagitis.

As with all medications, prescribing needs to be done thoughtfully and the pathophysiology of the signs and symptoms needs to be considered. We whole heartedly agree that there is a limited role for proton pump inhibitors in infants. Those infants with motility disorders and confirmed esophagitis do, however, merit therapy. Again, we assert that once prescribed, the benefit/risk ratio of long-term PPI treatment should be balanced, and the need of prolonged use of PPIs should be reassessed on a regular basis.

[*]Rachel L. Rosen, [†]Usha Krishnan, [‡]Hayat Mousa, [§]Luigi Dall'oglio, [||]Christophe Faure, and [¶]Frederic Gottrand
[*]*Division of Gastroenterology, Hepatology and Nutrition, Aerodigestive Center, Boston Children's Hospital, Boston, MA*
[†]*Department of Pediatric Gastroenterology, Sydney Children's Hospital, Discipline of Pediatrics, School of Women's and Children's Health, University of New South Wales, Sydney, Australia*
[‡]*Division of Pediatric Gastroenterology, Rady Children's Hospital, San Diego School of Medicine, University of California, San Diego, CA*
[§]*Digestive Endoscopy and Surgery Unit, Bambino Gesu Children's Hospital-IRCCS, Rome, Italy*
[||]*Division of Pediatric Gastroenterology, Department of Pediatrics, Sainte Justine Hospital, Université de Montréal, Montréal, Canada*
[¶]*Department of Pediatric Gastroenterology Hepatology and Nutrition, University Lille, National Reference Center for Congenital Malformation of the Esophagus, Lille, France*

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